Manuscript Title: A Public Health Perspective on 21st Century Risk Assessment

Authors: Maureen R. Gwinn, Daniel Axelrad, Tina Bahadori, David Bussard, Wayne Cascio, Kacee Deener, David Dix, Robert Kavlock, Thomas A Burke

Affiliation: US Environmental Protection Agency

Corresponding Author:

Maureen R. Gwinn, PhD DABT ATS
Office of Research and Development
1300 Pennsylvania Ave NW
MC 8101R
Washington, DC 20460
Office (202)564-4621
[HYPERLINK "mailto:gwinn.maureen@epa.gov"]

Acknowledgements:

Disclaimer: The views expressed in this paper are those of the authors and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.

Abstract

Preventing adverse health impacts from exposures to environmental chemicals is fundamental to protecting individual and public health. Chemical risk assessments inform environmental public health decisions by providing scientific information about the potential health effects following exposure to a chemical. When done efficiently and properly, risk assessment enables risk management actions that minimize the incidence and impacts of environmentally-induced diseases related to chemical exposure. However, traditional chemical risk assessment is faced with multiple challenges with respect to predicting and preventing disease in human populations. Epidemiological studies increasingly report observations of adverse health effects at exposure levels predicted from animal studies to be safe for humans, and often show effects that are not modeled or observed in animal studies. This discordance reinforces concerns about the adequacy of contemporary risk assessment practices [ADDIN EN.CITE <EndNote><Cite><Author>Birnbaum</Author><Year>2016</Year><RecNum>14</RecNum><DisplayText>(Birnbaum, Burke, & Jones, 2016)</DisplayText><record><rec-number>14</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1468526461">14</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Linda S. Birnbaum</author><author>Thomas A. Burke</author><author>James J. Jones</author></authors></contributors><titles><title>Informing 21st-Century Risk Assessments with 21st-Century Science</title><secondary-title>Environmental Health Perspectives</secondary-title></titles><periodical><full-title>Environmental Health Perspectives</full-title></periodical><pages>A60-A63</pages><volume>124</volume><number>4</number><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>] for protecting public health. Current advances in science and technology along with improved understanding of population health and disease – at times with individual precision – provide the opportunity to recast risk assessment and communication to protect public health. It is becoming clear that to protect public health more effectively, future risk assessments will need to use the full range of available data, draw on innovative methods to integrate diverse data streams, and consider health endpoints that also

reflect the range of subtle effects and morbidities observed in human populations (e.g., metabolic disorders, cardiovascular disease, childhood behavioral disorders, etc.). Given these factors, there is a need to reframe chemical risk assessment to be more clearly aligned with the public health goal of minimizing or preventing environmental exposures associated with disease.

Overview

For the past several decades, human health risk assessment has been a pillar of environmental health protection. In general, the products of risk assessment have been numerical risk values derived from animal toxicology studies of observable effects at high doses of individual chemicals. While this approach has contributed to our understanding of overt health outcomes from chemical exposures, it does not always match our understanding from epidemiology studies of the consequences of real world exposures in human populations, which are characterized by exposure to multiple pollutants, often chronically, at concentrations that can fluctuate over wide ranges; susceptible populations and lifestages; potential interactions between chemicals and nonchemical stressors and background disease states; and lifestyle factors that modify exposures (e.g., air tight houses).

Ten years ago, the National Research Council (NRC) offered a new paradigm for evaluating the safety of chemicals based on chemical characterization, testing using a toxicity pathway approach, and modeling and extrapolating the dose-response relationship from *in vitro* testing, all embedded in a risk context and considering population-based data and exposure [ADDIN EN.CITE <EndNote><Cite><Author>National Research Council</Author><Year>2007</Year><RecNum>10</RecNum><DisplayText>(National Research Council, 2007)</DisplayText><record><rec-number>10</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1468525960">10</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>National Research Council,</author></authors><tertiary-authors><author>The National Academies Press,</author></tertiary-authors></contributors><titles><title>Toxicity Testing in the 21st Century: A Vision and a Strategy</title></titles><dates><year>2007</year></dates><pub-

location>Washington, D.C.</pub-location><urls></urls></record></Cite></EndNote>]. Efforts such as the Tox21 consortium [ADDIN EN.CITE <EndNote><Cite><Author>Kavlock</Author><Year>2009</Year><RecNum>11</RecNum><DisplayText>(R. J. Kavlock, Austin, & Tice, 2009; Tice, Austin, Kavlock, & Bucher, 2013)</DisplayText><record><rec-number>11</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1468526016">11</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Robert J. Kavlock</author><author>Christopher P. Austin</author><author>Raymond Tice</author></authors></contributors><titles><title>Toxicity Testing in the 21st Century: Implications for Human Health Risk Assessment</title><secondary-title>Risk Anal</secondary-title></titles><periodical><full-title>Risk Anal</full-title></periodical><pages>485-497</pages><volume>29</volume><number>4</number><dates><year>2009</year></dates><urls></urls></record></Cite><Cite><Author>Tice</Author><Year>2013</Year><RecNum>5</RecNum><record><rec-number>5</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1468525644">5</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Raymond R. Tice</author><author>Christopher P. Austin</author><author>Robert J. Kavlock</author><author>John R. Bucher</author></authors></contributors><titles><title>Improving the Human Hazard Characterization of Chemicals: A Tox21 Update</title><secondary-title>Environmental Health Perspectives</secondary-title></titles><periodical><full-title>Environmental Health Perspectives</full-title></periodical><pages>756-765</pages><volume>121</volume><number>7</number><dates><year>2013</year></dates><urls></urls></record></Cite></EndNote>] and ToxCast program [ADDIN EN.CITE <EndNote><Cite><Author>Kavlock</Author><Year>2012</Year><RecNum>19</RecNum><DisplayText>(R. Kavlock et al., 2012)</DisplayText><record><rec-number>19</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1468527616">19</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Robert Kavlock</author><author>Kelly

Chandler</author><author>Keith Houck</author><author>Sid Hunter</author><author>Richard Judson</author><author>Nicole Kleinstreuer</author><author>Thomas Knudsen</author><author>Matt Martin</author><author>Stephanie Padilla</author><author>David Reif</author><author>Ann Richard</author><author>Daniel Rotroff</author><author>Nisha Sipes</author><author>David Dix</author></authors></contributors><titles><title>Update on EPA's ToxCast Program: Providing High Throughput Decision Support Tools for Chemical Risk Management</title><secondary-title>Chem Res Toxicol</secondary-title></titles><periodical><full-title>Chem Res Toxicol</full-title></periodical><pages>1287-1302</pages><volume>25</volume><number>7</number><dates><year>2012</year></dates><urls></urls></record></Cite></EndNote>] have helped us better understand the biological interactions of large numbers of chemicals using high-throughput assay systems, and we are witnessing early adoption of new technologies and approaches for screening chemicals for integrated testing [ADDIN EN.CITE <EndNote><Cite><Author>Browne</Author><Year>2015</Year><RecNum>18</RecNum><DisplayText>(Browne, Judson, Casey, Kleinstreuer, & Thomas, 2015)</DisplayText><record><rec-number>18</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1468527458">18</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Patience Browne</author><author>Richard S. Judson</author><author>Warren M. Casey</author><author>Nicole C. Kleinstreuer</author><author>Russell S. Thomas</author></authors></contributors><titles><title>Screening Chemicals for Estrogen Receptor Bioactivity Using a Computational Model</title><secondary-title>Environmental Science & Technology</secondary-title></titles><periodical><full-title>Environmental Science & Technology</full-title></periodical><pages>8804-8814</pages><volume>49</volume><number>14</number><dates><year>2015</year></dates><urls></urls></record></Cite></EndNote>].

Several other factors are also changing the way environmental health professionals think about chemical risks and how to most effectively protect public health. It is estimated that intrinsic factors (e.g., those that result in mutations due to random errors in DNA replication) account for only 10-30% of many common cancers [ADDIN EN.CITE <EndNote><Cite><Author>Wu</Author><Year>2016</Year><RecNum>20</RecNum><DisplayText>(Wu, Powers, Zhu, & Hannun, 2016)</DisplayText><record><rec-number>20</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1470317090">20</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Song Wu</author><author>Scott Powers</author><author>Wei Zhu</author><author>Yusuf A. Hannun	</author></authors></contributors><titles><title>Substantial contribution of extrinsic risk factors to cancer development</title><secondary-title>Nature</secondary-title></titles><periodical><full-title>Nature</full-title></periodical><pages>43-47</pages><volume>529</volume><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>]. Similarly, only 30-40% of birth defects can be attributed to known causes such as genetics, fetal alcohol syndrome, maternal smoking, and folate insufficiency [ADDIN EN.CITE <EndNote><Cite><Author>Weinhold</Author><Year>2009</Year><RecNum>3</RecNum><DisplayText>(Weinhold, 2009)</DisplayText><record><rec-number>3</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1468525478">3</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>B. Weinhold</author></authors></contributors><titles><title>Environmental Factors in Birth Defects: What We Need to Know</title><secondary-title>Environmental Health Perspectives</secondary-title></titles><periodical><full-title>Environmental Health Perspectives</full-title></periodical><pages>A440-A447</pages><volume>117</volume><number>10</number><dates><year>2009</year></dates><urls></urls></record></Cite></EndNote>]. Other studies have concluded that non-genetic environmental factors and gene by environment interactions are the primary causes of chronic

diseases [ADDIN EN.CITE <EndNote><Cite><Author>Rappaport</Author><Year>2011</Year><RecNum>21</RecNum><DisplayText>(Rappaport, 2011; Rappaport, Barupal, Wishart, Vineis, & Scalbert, 2014)</DisplayText><record><rec-number>21</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1470317192">21</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Stephen M. Rappaport</author></authors></contributors><titles><title>Implications of the exposome for exposure science</title><secondary-title>Journal of Exposure Science and Environmental Epidemiology</secondary-title></titles><periodical><full-title>Journal of Exposure Science and Environmental Epidemiology</full-title></periodical><pages>5-9</pages><volume>21</volume><dates><year>2011</year></dates><urls></urls></record></Cite><Cite><Author>Rappaport</Author><Year>2014</Year><RecNum>22</RecNum><record><rec-number>22</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1470317303">22</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Stephen M. Rappaport</author><author>Dinesh K. Barupal</author><author>David Wishart</author><author>Paolo Vineis</author><author>Augustin Scalbert</author></authors></contributors><titles><title>The Blood Exposome and Its Role in Discovering Causes of Disease</title><secondary-title>Environmental Health Perspectives</secondary-title></titles><periodical><full-title>Environmental Health Perspectives</full-title></periodical><pages>769-774</pages><volume>122</volume><dates><year>2014</year></dates><urls></urls></record></Cite></EndNote>]. The ability to evaluate and quantify the role of environmental factors on public health is a clear opportunity, but it is limited by the lack of readily available models for prominent clinical outcomes.

Current challenges in predicting risk from exposure to environmental chemicals

Understanding public health risk from environmental chemical exposures is complicated by many factors, such as population variability and susceptibility, which are poorly understood and difficult to characterize and incorporate into risk assessments. For example, a person's unique microbiome may modulate his/her response to environmental exposures [ADDIN EN.CITE <EndNote><Cite><Author>Dietert</Author><Year>2015</Year><RecNum>25</RecNum><DisplayText>(Dietert & Silbergeld, 2015; Patterson & Turnbaugh, 2014)</DisplayText><record><rec-number>25</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1470317694">25</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Rodney Reynolds Dietert</author><author>Ellen Kovner Silbergeld</author></authors></contributors><titles><title>Biomarkers for the 21st Century: Listening to the Microbiome</title><secondary-title>Toxicological Sciences</secondary-title></titles><periodical><full-title>Toxicological Sciences</full-title></periodical><pages>208-216</pages><volume>144</volume><number>2</number><dates><year>2015</year></dates><urls></urls></record></Cite><Cite><Author>Patterson</Author><Year>2014</Year><RecNum>24</RecNum><record><rec-number>24</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1470317566">24</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Andrew D. Patterson</author><author>Peter J. Turnbaugh</author></authors></contributors><titles><title>Microbial Determinants of Biochemical Individuality and Their Impact on Toxicology and Pharmacology</title><secondary-title>Cell Metabolism</secondary-title></titles><periodical><full-title>Cell Metabolism</full-title></periodical><pages>761-768</pages><volume>20</volume><number>5</number><dates><year>2014</year></dates><urls></urls></record></Cite></EndNote>]. Although studies are limited in this emerging area, knowledge about the microbiome may inform interindividual variability and unexplained susceptibility observed in populations. Scientists have begun to appreciate the role of the microbiome in the lack of reproducibility and interpretability of animal studies [ADDIN EN.CITE <EndNote><Cite><Author>Servick</Author><Year>2016</Year><RecNum>43</RecNum><Displ

ayText>(Servick, 2016)</DisplayText><record><rec-number>43</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1472143865">43</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Kelly Servick</author></authors></contributors><titles><title>Of mice and microbes</title><secondary-title>Science</secondary-title></titles><periodical><full-title>Science</full-title></periodical><pages>741-743</pages><volume>353</volume><number>6301</number><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>]. Other examples of important factors to incorporate in risk assessments can be found in Table 1.

Table 1. Examples of current risk assessments challenges and opportunities

Risk Assessment Challenge	Description	Impact on Risk Assessment	Public Health Opportunity
Microbiome	Microorganisms that reside within and on our bodies and how they interact with the environment	Exposure modification; Susceptibility/resilience to environmental pollutants; Important as an early life determinant of health; Potential role in allergic response, asthma	Potential targets for prevention and intervention, management of allergic responses, and precision risk management
Nonchemical Stressors	Physical and psychosocial stressors, including noise, temperature, socioeconomic status, social stress, and limited resources	Impact on baseline susceptibility and response to environmental exposures (effect modification)	Potential role in cumulative assessment and improved identification and assessment of vulnerable populations; potential target for public health interventions (e.g., stress management)
Early life determinants of health	Biological characteristics and exposures that can	Critical life stage for exposures and developmental health	Potential for early-life interventions for prevention and

	determine chronic and life-long health outcomes	outcomes. Impact of exposures during early-life may play a role in later disease states (e.g., endocrine disruptors, epigenetic changes, microbiome)	management of later disease
Background exposures	Chronic population exposures to a myriad of environmental chemicals	Exposures to "background" chemicals may impact response to "target" chemical exposures and may change population health baselines	Increased public health protection if baseline exposures are taken into account
Baseline health status	Individual health status, with a focus on potential health susceptibilities that may alter response to environmental chemical exposures	Baseline health status may impact response to additional exposures	Increased public health protection if baseline health status is taken into account
Molecular initiating events and subsequent key events in adverse outcomes pathways	Early biological changes or precursor effects in response to chemical exposures may be identified by *in vitro*, animal or epidemiological studies	To be meaningful for decision-makers, it is useful to have qualitative and quantitative understanding of ultimate health impact of early biological changes	Improved public health protection without need for long-term toxicology or epidemiology studies

213

214 **Opportunities for leveraging multiple data types for public health protection**

215 Concurrent with these challenges, science and technology are advancing rapidly and in ways that
216 create opportunities for risk assessment. Public health disciplines help us understand how
217 baseline health status can influence the impact of population level chemical exposures. We also
218 need to consider how environmental pollutants may contribute to overall disease burden for
219 endpoints not traditionally considered in chemical risk assessment (e.g., metabolic disorders).
220 New methods in epidemiological research help us evaluate complex interactions among

multifactorial causes of disease ranging from macro (societal, neighborhood) to micro (molecular) factors, relevance of exposures during sensitive lifestages, and a better understanding of interrelatedness of disease across lifespan [ADDIN EN.CITE <EndNote><Cite><Author>Louis</Author><Year>2015</Year><RecNum>27</RecNum><DisplayText>(Louis et al., 2015)</DisplayText><record><rec-number>27</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1470317909">27</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Germaine M. Buck Louis</author><author>Michael S. Bloom</author><author>Nicolle M. Gatto</author><author>Carol R. Hogue</author><author>Daniel J.Westreich</author><author>Cuilin Zhang</author></authors></contributors><titles><title>Epidemiology's Continuing Contribution to Public Health: The Power of "Then and Now"</title><secondary-title>American Journal of Epidemiology</secondary-title></titles><periodical><full-title>American Journal of Epidemiology</full-title></periodical><pages>e1-e8</pages><volume>181</volume><number>8</number><dates><year>2015</year></dates><urls></urls></record></Cite></EndNote>]. Advances in high-throughput technologies and computational modeling (e.g., ToxCast, Tox21, and ExpoCast efforts) are providing data on hazard and exposure potential for a large number of data-poor chemicals. One approach with potential to advance our understanding of how chemical exposures can impact health is the use of adverse outcome pathways (AOPs), which integrate various types of biological information to link molecular initiating events to downstream key events and ultimately unwanted health outcomes [ADDIN EN.CITE ADDIN EN.CITE.DATA]. To fully realize the potential of AOP-based approaches and to integrate biological findings across disciplines, we must strengthen our ability to detect precursor events in human populations and identify biologically-relevant exposure metrics, ideally measurable in individuals.

Effectively predicting population risk by integrating a variety of data streams (e.g., epidemiology, toxicology, high-throughput testing) and considering multiple sources and pathways of exposure can better inform environmental public health decisions. Advances in technology and computational capabilities have fostered new opportunities for generating and analyzing

molecular, animal, and human data on effects and exposures, which can be integrated into chemical risk assessments. At the same time, probabilistic and high-throughput approaches for risk assessment have been advancing. Table 2 highlights various data types available and challenges applying these data types to inform risk assessment.

Table 2. Data streams and opportunities and challenges for informing risk assessment

Data Type	Description	Opportunity	Challenge
Non-testing data	Non-testing approaches, such as quantitative structure-activity relationship (QSAR) models and read-across allo	Advances in development of chemical libraries, cheminformatics and read-across predictions and integration with molecular data and AOPs have significantly improved their application and predictive capacity [ADDIN EN.CITE ADDIN EN.CITE.DATA].	Challenges remain for developing principles for acceptance; for characterizing and incorporating uncertainties into predictions; and for developing objective metrics of performance [ADDIN EN.CITE <EndNote><Cite><Author>Patlewicz</Author><Year>2016</Year><RecNum>34</RecNum><DisplayText>(Patlewicz & Fitzpatrick, 2016)</DisplayText><record><rec-number>34</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1470319881">34</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Grace Patlewicz</author><author>Jeremy M. Fitzpatrick </author></authors></contributors><titles><title><style face="normal" font="default" size="100%">Current and Future Perspectives on the Development, Evaluation, and Application of </style><style face="italic" font="default" size="100%">in Silico </style><style face="normal" font="default"

	w us to pre dict toxi city whe re ade qua te testi ng data are abs ent.		size="100%">Approaches for Predicting Toxicity</style></title><secondary-title>Chemical Research in Toxicology</secondary-title></titles><periodical><full-title>Chemical Research in Toxicology</full-title></periodical><pages>438-451</pages><volume>29</volume><number>4</number><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>].
M ol ec ul ar	Mol ecul ar data , incl udin g bioa ctivi ty bioc hem ical and cell-bas ed *in vitr o* assa y data and a	Biochemical and cell-based *in vitro* assay data, for example, can identify mechanism-based molecular targets and biological pathways (e.g., AOPs) and can help inform our understanding of the health outcomes of environmental exposures, using data that are potentially more human relevant.	Lack of scientific consensus as yet on inferring hazard from bioactivity *in vitro* assay and omics-based data and providing quantitative dose-response information in exposure metrics usable for risk assessment and policymaking

	range of 'omics-based' data that characterize thousands of chemicals with potential environmental exposures.		
Animal	Traditional animal testing provides a hazard based poin	For only a handful of chemicals, there are a large quantity of traditional animal testing data and the risk assessment community has decades of experience in using these types of data.	There are potentially large uncertainties associated with using traditional animal testing to estimate risk. For example, extrapolating from animal to human; accounting for human population variability and lifestage susceptibility; and from high to low doses. Many chemicals lack sufficient animal testing, and tests that are conducted may fail to identify effects that occur in humans. Qualitative and quantitative variability in animal tests [ADDIN EN.CITE <EndNote><Cite><Author>Kleinstreuer</Author><Year>2016</Year><RecNu

	t of dep artu re for risk asse ssm ents .		m>44</RecNum><DisplayText>(Kleinstreuer et al., 2016)</DisplayText><record><rec-number>44</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1472144040">44</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Nicole C. Kleinstreuer</author><author>Patricia C. Ceger</author><author>David G. Allen</author><author>Judy Strickland</author><author>Xiaoqing Chang</author><author>Jonathan T. Hamm</author><author>Warren M. Casey</author></authors></contributors><titles><title>A Curated Database of Rodent Uterotrophic Bioactivity</title><secondary-title>Environ Health Perspect</secondary-title></titles><periodical><full-title>Environ Health Perspect</full-title></periodical><pages>556-562</pages><volume>124</volume><number>5</number><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>].
H u m an	Epid emi olog ical and oth er hu man data sup port holi	Numerous examples exist demonstrating the value of human data relative to animal testing results, wherein the human studies indicate adverse effects at exposure levels predicted to be safe based on animal studies [ADDIN EN.CITE <EndNote><Cite><Author>Birnbaum</Author><Year>2016</Year><RecNum>14</RecNum><DisplayText>(Birnbaum et al., 2016)</DisplayText><record><rec-number>14</rec-number><foreign-keys><key app="EN" db-	Oftentimes human studies are limited in providing mechanistic and dose-response data, emphasizing the complementarity of human, animal and molecular data. Exposure misclassification, when present, biases results to the null. Possibility of unmeasured confounders often undermines confidence in observed associations, and it may require multiple studies and many years to rule out chance, bias and

	stic asse ssm ent of the effe cts of che mic al exp osur es on publ ic heal th.	id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1468526461">14</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Linda S. Birnbaum</author><author>Thomas A. Burke</author><author>James J. Jones</author></authors></contributors><titles><title>Informing 21st-Century Risk Assessments with 21st-Century Science</title><secondary-title>Environmental Health Perspectives</secondary-title></titles><periodical><full-title>Environmental Health Perspectives</full-title></periodical><pages>A60-A63</pages><volume>124</volume><number>4</number><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>]. Newer exposure science and statistical techniques advance the understanding of human variability that can be obtained from epidemiology and individual sequencing. Epidemiology is the most informative method for understanding effect modification by nonchemical stressors and baseline health status.	confounding as possible explanations for observed associations.
Ex po su re	Exp osur e char acte rizat ion is imp rove d to capt ure	Advances in exposure science, including targeted and non-targeted biomonitoring, application of sensors and other new technologies are greatly advancing general population exposure characterization. High-throughput exposure models allow exposure predictions on thousands of chemicals with associated uncertainty [ADDIN EN.CITE <EndNote><Cite><Author>Wambaugh</Author><Year>2014</Year><RecNum>29</RecNum><DisplayText>(Wambaug	Understanding how to estimate and incorporate the inter- and intra-individual variability in exposures into current designs of toxicity testing and risk assessments. Extrapolating relevant target tissue/organ dose information from external exposures and from in vitro assays. Accounting for multiple exposures; sample collection, data management and analysis; covering or extrapolating to a broader chemical space, since we lack

	the variability in time, space, and within and across populations. Better toxicokinetic data link external to internal dosimetry, and relevant environmental exposure con	h et al., 2014)</DisplayText><record><rec-number>29</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1470318924">29</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>John F. Wambaugh</author><author>Anran Wang</author><author>Kathie L. Dionisio</author><author>Alicia Frame</author><author>Peter Egeghy</author><author>Richard Judson</author><author>R. Woodrow Setzer</author></authors></contributors><titles><title>High Throughput Heuristics for Prioritizing Human Exposure to Environmental Chemicals</title><secondary-title>Environmental Science & Technology</secondary-title></titles><periodical><full-title>Environmental Science & Technology</full-title></periodical><pages>12760-12767</pages><volume>48</volume><number>21</number><dates><year>2014</year></dates><urls></urls></record></Cite></EndNote>]. More timely data provides opportunities for better intervention and exposure and risk mitigation strategies [ADDIN EN.CITE <EndNote><Cite><Author>Donald</Author><Year>2016</Year><RecNum>45</RecNum><DisplayText>(Donald et al., 2016)</DisplayText><record><rec-number>45</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs"	biomarkers for many environmental chemicals.

	centrations with biological significance. Non-targeted chemical analyses identify previously unknown exposures. Applications of sensors allows for collection of	timestamp="1472144470">45</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Carey E. Donald</author><author>Richard P. Scott</author><author>Kathy L. Blaustein</author><author>Mary L. Halbleib</author><author>Makhfousse Sarr</author><author>Paul C. Jepson</author><author>Kim A. Anderson</author></authors></contributors><titles><title>Silicone wristbands detect individuals' pesticide exposures in West Africa</title><secondary-title>R Soc open sci</secondary-title></titles><periodical><full-title>R Soc open sci</full-title></periodical><pages>160433</pages><volume>3</volume><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>].	

	more timely exposure information.		
Digital Data	Data from mobile, social, real-time sources. The ongoing revolution in social media use and communication has pro	A significant source of untapped data.	The collection and application of these data have significant ethical implications that need to be understood and managed. Methods to evaluate the quality of the data and build confidence in the applications need to be developed.

	vided a new source of data used in exposure science and environmental epidemiology for local and timely harvesting of information about disease and health dyn		

	amics in populations around the world.		

255

256 **A public health perspective for chemical risk assessment**

257 A public health perspective for chemical risk assessment would approach risk assessment from a
258 new lens. It would address population health with a focus on health and societal burden of
259 disease; use and integrate all available types of data – including traditional toxicology, human
260 epidemiological findings, as well as newer and emerging data streams and information, such as
261 digital epidemiology [ADDIN EN.CITE
262 <EndNote><Cite><Author>Bakker</Author><Year>2016</Year><RecNum>47</RecNum><Displ
263 ayText>(Bakker, Martinez-Bakker, Helm, & Stevenson, 2016; Salathé et al.,
264 2012)</DisplayText><record><rec-number>47</rec-number><foreign-keys><key app="EN" db-
265 id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1472144804">47</key></foreign-
266 keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Kevin
267 M. Bakker</author><author>Micaela Elvira Martinez-Bakker</author><author>Barbara
268 Helm</author><author>Tyler J.
269 Stevenson</author></authors></contributors><titles><title>Digital epidemiology reveals global
270 childhood disease seasonality and the effects of immunization</title><secondary-
271 title>PNAS</secondary-title></titles><periodical><full-title>PNAS</full-
272 title></periodical><pages>6689-
273 6694</pages><volume>113</volume><number>24</number><dates><year>2016</year></dat
274 es><urls></urls></record></Cite><Cite><Author>Salathé</Author><Year>2012</Year><RecNu
275 m>46</RecNum><record><rec-number>46</rec-number><foreign-keys><key app="EN" db-
276 id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1472144671">46</key></foreign-

277 keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Marcel
278 Salathé</author><author>Linus Bengtsson</author><author>Todd J.
279 Bodnar</author><author>Devon D. Brewer</author><author>John S.
280 Brownstein</author><author>Caroline Buckee</author><author>Ellsworth M.
281 Campbell</author><author>Ciro Cattuto</author><author>Shashank
282 Khandelwal</author><author>Patricia L. Mabry</author><author>Alessandro Vespignani
283 </author></authors></contributors><titles><title>Digital Epidemiology</title><secondary-
284 title>PLoS Comput Biol</secondary-title></titles><periodical><full-title>PLoS Comput Biol</full-
285 title></periodical><pages>e1002616</pages><volume>8</volume><number>7</number><dat
286 es><year>2012</year></dates><urls></urls></record></Cite></EndNote>], high-throughput
287 data, and adverse outcome pathways; and draw on public health approaches, such as
288 attributable risk or relative risk. This new perspective may be especially important for some
289 historically challenging aspects of risk assessment, such as understanding cumulative risks of
290 exposures to multiple chemical and non-chemical stressors. Internationally, scientists have raised
291 concerns about the large number of ubiquitous chemicals people are exposed to and called for
292 rethinking approaches to evaluating the health impacts of chemicals (Goodson et al. [ADDIN
293 EN.CITE ADDIN EN.CITE.DATA] Bennett et al. 2016). Figure 1 presents a conceptual model for
294 a public health perspective for risk assessment.
295
296 While approaching assessments from the perspective of health outcomes may be challenging, it
297 provides the opportunity to evaluate exposures and effects across the lifespan that are relevant
298 to population health. Advances in science and technology – such as AOP development (OECD
299 website), the broader availability of chemical and biological data, and the applications of
300 statistical and bioinformatics tools bring this previously aspirational approach well within reach [
301 ADDIN EN.CITE
302 <EndNote><Cite><Author>Rom</Author><Year>2013</Year><RecNum>49</RecNum><Display
303 Text>(Rom, Boushey, & Caplan, 2013)</DisplayText><record><rec-number>49</rec-
304 number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs"
305 timestamp="1472145433">49</key></foreign-keys><ref-type name="Journal Article">17</ref-

306 type><contributors><authors><author>William N. Rom</author><author>Homer
307 Boushey</author><author>Arthur
308 Caplan</author></authors></contributors><titles><title>Experimental Human Exposure to Air
309 Pollutants Is Essential to Understand Adverse Health Effects</title><secondary-title>Am J Respir
310 Cell Mol Biol</secondary-title></titles><periodical><full-title>Am J Respir Cell Mol Biol</full-
311 title></periodical><pages>691-
312 696</pages><volume>49</volume><number>5</number><dates><year>2013</year></dates>
313 <urls></urls></record></Cite></EndNote>].
314
315
316 **Illustrative Example: Cardiovascular Disease**

317 The following example illustrates how a public health approach may inform the challenge of
318 cardiovascular disease. Cardiovascular disease is the number one cause of mortality worldwide
319 and is a major U.S. public health burden [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Annual costs
320 of cardiovascular disease in the U.S. were estimated to be $317 million in 2011-2012, considering
321 direct medical costs and lost productivity due to premature mortality (Mozaffarian et al., 2016).
322 This estimate is likely to substantially underestimate the social cost of cardiovascular disease,
323 due to limitations in estimation of indirect costs associated with morbidity and premature
324 mortality (U.S. EPA 2010). While much is known about the biochemical and behavioral risk factors
325 associated with cardiovascular disease, particularly in comparison with other diseases and health
326 conditions, the traditional risk factors fail to account for 10 to 25 percent of its prevalence [
327 ADDIN EN.CITE
328 <EndNote><Cite><Author>Kannel</Author><Year>2009</Year><RecNum>13</RecNum><Displ
329 ayText>(Kannel & Vasan, 2009)</DisplayText><record><rec-number>13</rec-
330 number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs"
331 timestamp="1468526291">13</key></foreign-keys><ref-type name="Journal Article">17</ref-
332 type><contributors><authors><author>William B. Kannel</author><author>Ramachandran S.
333 Vasan</author></authors></contributors><titles><title>Adverse Consequences of the 50%
334 Misconception</title><secondary-title>Am J Cardiol</secondary-

title></titles><periodical><full-title>Am J Cardiol</full-title></periodical><pages>426-427</pages><volume>103</volume><number>3</number><dates><year>2009</year></dates><urls></urls></record></Cite></EndNote>]. Environmental factors including air pollution [ADDIN EN.CITE <EndNote><Cite><Author>Kaufman</Author><Year>2016</Year><RecNum>12</RecNum><DisplayText>(Kaufman et al., 2016)</DisplayText><record><rec-number>12</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1468526230">12</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Joel D Kaufman</author><author>Sara D Adar</author><author>R Graham Barr</author><author>Matthew Budoff</author><author>Gregory L Burke</author><author>Cynthia L Curl</author><author>Martha L Daviglus</author><author>Ana V Diez Roux</author><author>Amanda J Gassett</author><author>David R Jacobs Jr</author><author>Richard Kronmal</author><author>Timothy V Larson</author><author>Ana Navas-Acien</author><author>Casey Olives</author><author>Paul D Sampson</author><author>Lianne Sheppard</author><author>David S Siscovick</author><author>James H Stein</author><author>Adam A Szpiro</author><author>Karol E Watson</author></authors></contributors><titles><title>Association between air pollution and coronary artery calcification within six metropolitan areas in the USA (the Multi-Ethnic Study of Atherosclerosis and Air Pollution): a longitudinal cohort study</title><secondary-title>The Lancet</secondary-title></titles><periodical><full-title>The Lancet</full-title></periodical><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>] and chemical exposures [ADDIN EN.CITE <EndNote><Cite><Author>Kirkley</Author><Year>2014</Year><RecNum>53</RecNum><DisplayText>(Kirkley & Sargis, 2014)</DisplayText><record><rec-number>53</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1472146476">53</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Andrew G. Kirkley</author><author>Robert M.

Sargis</author></authors></contributors><titles><title>Environmental Endocrine Disruption of Energy Metabolism and Cardiovascular Risk</title><secondary-title>Curr Diab Rep</secondary-title></titles><periodical><full-title>Curr Diab Rep</full-title></periodical><pages>494</pages><volume>14</volume><number>6</number><dates><year>2014</year></dates><urls></urls></record></Cite></EndNote>] are thought to contribute to the unexplained fraction. While mortality due to cardiovascular disease has decreased over the last few decades in the developed world due to reductions in behavioral risk factors, the rising prevalence of obesity and diabetes might account for the deceleration in the rate of improvement in annual cardiovascular mortality in the U.S. over the last few years [ADDIN EN.CITE <EndNote><Cite><Author>Sidney</Author><Year>2016</Year><RecNum>54</RecNum><DisplayText>(Sidney, Quesenberry et al. 2016)</DisplayText><record><rec-number>54</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1472146661">54</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Sidney, S</author><author>Quesenberry,, Jr., CP</author><author>Jaffe, MG</author><author>Sorel, M</author><author>Nguyen-Huynh, MN</author><author>Kushi, LH</author><author>Go, AS</author><author>Rana, JS</author></authors></contributors><titles><title>Recent Trends in Cardiovascular Mortality in the United States and Public Health Goals</title><secondary-title>JAMA Cardiol</secondary-title></titles><periodical><full-title>JAMA Cardiol</full-title></periodical><pages>594-599</pages><volume>1</volume><number>5</number><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>].

There is an urgent need to better understand the biological pathways through which environmental exposures to chemical and non-chemical stressors act to stimulate and accelerate atherosclerosis and promote adverse cardiovascular health effects. Applying the adverse outcome pathway framework [ADDIN EN.CITE <EndNote><Cite><Author>Cosselman</Author><Year>2015</Year><RecNum>35</RecNum><DisplayText>(Cosselman, Navas-Acien, & Kaufman, 2015)</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-

id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1470320174">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Kristen E. Cosselman</author><author>Ana Navas-Acien</author><author>Joel D. Kaufman</author></authors></contributors><titles><title>Environmental factors in cardiovascular disease</title><secondary-title>Nature Reviews Cardiology</secondary-title></titles><periodical><full-title>Nature Reviews Cardiology</full-title></periodical><pages>627-642</pages><volume>12</volume><dates><year>2015</year></dates><urls></urls></record></Cite></EndNote>], the initial molecular response to a chemical exposure will often be receptor activation and changes in metabolism, and ultimately changes in tissue and organ function. Such changes can be modified by both intrinsic (e.g., sex, age, genetic and epigenetic background) and extrinsic factors (e.g., co-exposures to other chemical and non-chemical stressors). Over time, these changes produce subclinical effects such as changes in electrical and mechanical cardiac function, vascular function, and non-obstructive atherosclerotic vascular changes. With persistence of metabolic changes that stimulate the progression of vascular disease, clinical cardiovascular events such as heart attacks, strokes, heart failure, and abnormal heart rhythms follow.

To date, the most comprehensive application of this approach has been in the study of population level health effects of air pollution exposure [ADDIN EN.CITE <EndNote><Cite><Author>Cosselman</Author><Year>2015</Year><RecNum>35</RecNum><DisplayText>(Cosselman et al., 2015)</DisplayText><record><rec-number>35</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1470320174">35</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Kristen E. Cosselman</author><author>Ana Navas-Acien</author><author>Joel D. Kaufman</author></authors></contributors><titles><title>Environmental factors in cardiovascular disease</title><secondary-title>Nature Reviews Cardiology</secondary-title></titles><periodical><full-title>Nature Reviews Cardiology</full-title></periodical><pages>627-

642</pages><volume>12</volume><dates><year>2015</year></dates><urls></urls></record></Cite></EndNote>]. Epidemiological data at the population level has provided unequivocal proof that air pollutant exposure (e.g., ambient particular matter and NO_2) accelerates the development and progression of coronary atherosclerosis [ADDIN EN.CITE <EndNote><Cite><Author>Kaufman</Author><Year>2016</Year><RecNum>12</RecNum><DisplayText>(Kaufman et al., 2016)</DisplayText><record><rec-number>12</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1468526230">12</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Joel D Kaufman</author><author>Sara D Adar</author><author>R Graham Barr</author><author>Matthew Budoff</author><author>Gregory L Burke</author><author>Cynthia L Curl</author><author>Martha L Daviglus</author><author>Ana V Diez Roux</author><author>Amanda J Gassett</author><author>David R Jacobs Jr</author><author>Richard Kronmal</author><author>Timothy V Larson</author><author>Ana Navas-Acien</author><author>Casey Olives</author><author>Paul D Sampson</author><author>Lianne Sheppard</author><author>David S Siscovick</author><author>James H Stein</author><author>Adam A Szpiro</author><author>Karol E Watson</author></authors></contributors><titles><title>Association between air pollution and coronary artery calcification within six metropolitan areas in the USA (the Multi-Ethnic Study of Atherosclerosis and Air Pollution): a longitudinal cohort study</title><secondary-title>The Lancet</secondary-title></titles><periodical><full-title>The Lancet</full-title></periodical><dates><year>2016</year></dates><urls></urls></record></Cite></EndNote>]. Xenobiotic metals such as arsenic, cadmium, lead, and mercury are also associated with atherosclerosis [ADDIN EN.CITE <EndNote><Cite><Author>Solenkova</Author><Year>2014</Year><RecNum>6</RecNum><DisplayText>(Solenkova et al., 2014)</DisplayText><record><rec-number>6</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1468525712">6</key></foreign-keys><ref-type name="Journal Article">17</ref-

type><contributors><authors><author>Natalia V. Solenkova</author><author>Jonathan D. Newman</author><author>Jeffrey S. Berger</author><author>George Thurston</author><author>Judith S. Hochman</author><author>Gervasio A. Lamas</author></authors></contributors><titles><title>Metal Pollutants and Cardiovascular Disease: Mechanisms and Consequences of Exposure</title><secondary-title>Am Heart J</secondary-title></titles><periodical><full-title>Am Heart J</full-title></periodical><pages>812-822</pages><volume>168</volume><number>6</number><dates><year>2014</year></dates><urls></urls></record></Cite></EndNote>]. Gene-environment interaction alters risk of vascular disease [ADDIN EN.CITE <EndNote><Cite><Author>Zanobetti</Author><Year>2011</Year><RecNum>2</RecNum><DisplayText>(Zanobetti, Baccarelli, & Schwartz, 2011)</DisplayText><record><rec-number>2</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1468525348">2</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>A. Zanobetti</author><author>A. Baccarelli</author><author>J. Schwartz</author></authors></contributors><titles><title>Gene-air pollution interaction and cardiovascular disease: a review</title><secondary-title>Prog Cardiovasc Dis</secondary-title></titles><periodical><full-title>Prog Cardiovasc Dis</full-title></periodical><pages>344-352</pages><volume>53</volume><number>5</number><dates><year>2011</year></dates><urls></urls></record></Cite></EndNote>]; for example, the residential proximity to highways (representing exposure to a mixture of traffic-related air pollutants) is associated with peripheral vascular disease, which is modified by the gene encoding bone morphogenic protein 8 [ADDIN EN.CITE <EndNote><Cite><Author>Ward-Caviness</Author><Year>2016</Year><RecNum>4</RecNum><DisplayText>(Ward-Caviness et al., 2016)</DisplayText><record><rec-number>4</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1468525581">4</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Cavin K. Ward-Caviness</author><author>Lucas M. Neas</author><author>Colette

480 Blach</author><author>Carol S. Haynes</author><author>Karen LaRocque-
481 Abramson</author><author>Elizabeth Grass</author><author>Elaine
482 Dowdy</author><author>Robert B. Devlin</author><author>David Diaz-
483 Sanchez</author><author>Wayne E. Cascio</author><author>Marie Lynn
484 Miranda</author><author>Simon G. Gregory</author><author>Svati H.
485 Shah</author><author>William E. Kraus</author><author>Elizabeth R.
486 Hauser</author></authors></contributors><titles><title>Genetic Variants in the Bone
487 Morphogenic Protein Gene Family Modify the Association between Residential Exposure to
488 Traffic and Peripheral Arterial Disease</title><secondary-title>PLoS ONE</secondary-
489 title></titles><periodical><full-title>PLoS ONE</full-
490 title></periodical><volume>11</volume><number>4</number><dates><year>2016</year></d
491 ates><urls></urls></record></Cite></EndNote>]. Given the complexity of the drivers of
492 atherosclerosis, a medical model treating blood pressure and high cholesterol and advising
493 dietary modification and exercise will be inadequate to fully address this disease. Likewise
494 identifying the chemicals that increase risk on an individual basis will be inadequate to prevent
495 vascular disease. Instead an integrated systems approach is needed to fully account for all known
496 risk factors and formulate the problem to define the most effective strategy to decrease
497 individual risk and societal burden. Accomplishing this will require clinical data that fully reflects
498 a population under consideration as well as exposures to traditional risk factors, biomonitoring
499 data documenting exposures to multiple chemicals, and molecular responses from *in vitro* and *in*
500 *vivo* studies indicative of the activation of biochemical pathways that accelerate atherosclerosis.

501 While this approach might appear inconceivable, it is not unrealistic. Our proposed innovative
502 approach to chemical risk assessment is occurring contemporaneously during the formative
503 stages of the NIH-sponsored Precision Medicine Initiative that will drive integration of genomics,
504 data sciences and bioinformatics as the basis for improved individual health care, disease
505 prevention and public health. The Affordable Care Act has accelerated electronic medical record
506 adoption within healthcare practices and hospital systems potentially offering a valuable source
507 of information for population level health monitoring. Recent research has used Big Data to study
508 the early stages of disease and better classify and predict disease progression and could be used

to inform personalized medicine to optimize wellness in healthy populations [ADDIN EN.CITE ADDIN EN.CITE.DATA]. Moreover, the anticipated integration and development of technologies and analytical tools have the potential to improve public health and increase the spatial and temporal resolution of environmental health surveillance. The establishment of a long-term representative precision medicine cohort, if integrated with the proposed National Biomonitoring Network [ADDIN EN.CITE <EndNote><Cite ExcludeAuth="1"><Author>Association of Public Health Laboratories (APHL)</Author><Year>2015</Year><RecNum>57</RecNum><Prefix>APHL </Prefix><DisplayText>(APHL 2015)</DisplayText><record><rec-number>57</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1472147337">57</key></foreign-keys><ref-type name="Report">27</ref-type><contributors><authors><author>Association of Public Health Laboratories (APHL),</author></authors></contributors><titles><title>National Biomonitoring Plan. November 2015.</title></titles><dates><year>2015</year></dates><urls><related-urls><url>https://www.aphl.org/aboutAPHL/publications/Documents/EH_National_Biomonitoring_Plan_112015.pdf</url></related-urls></urls></record></Cite></EndNote>], could have enormous benefit in understanding the relationship between chemical exposures and disease and in managing some of the most challenging clinical problems more effectively. Applying this framework would potentially expand our understanding of the origins of vascular disease and its progression, help define strategies for primary prevention to thwart the initiation of the process we ultimately call atherosclerosis. Thus, such a framework will provide new and ongoing insights into the associations between environmental exposures that contribute the greatest burden to public health. This approach would facilitate accounting for sensitive populations and could inform suggested individual health or behavioral measures where there has been past exposures or where current exposure cannot be reduced enough to protect those most at risk.

Discussion

The proposed conceptual model is grounded in public health principles and focused on identifying the greatest opportunity to reduce environmental exposures to improve health outcomes. Along with traditional risk assessment, this perspective can better inform public

health decision making. While there are clear benefits to operating within a public health-focused framework and moving away from individual chemicals and apical endpoints, there are also challenges.

Informing decision-making: Since the 1980s, EPA's decision-making has been based on traditional risk assessments that are conducted within the constraints of EPA's statutes and programs. While program-targeted risk assessments will remain an important component, the disease-based approach draws upon information in a holistic fashion that cuts across organizational and legal boundaries, integrating traditional inputs with newer data streams. These assessments will provide decision-makers with critical information to inform exposure reduction efforts to impact the selected health outcomes, and ultimately, improve public health. Because those exposure reduction efforts would take place within the existing statutory construct, an important implementation step would be to move from findings of disease-based risk assessments to assessments of specific risk management actions under the relevant statutory authorities.

Priorities for screening and testing: A health outcome-focused framework can inform priorities for screening and testing the toxicity of chemicals. Efforts to develop and synthesize approaches for screening large numbers of chemicals using high-throughput toxicity testing and exposure prediction should continue to provide data for data-poor chemicals. For example, in the recently announced Cancer Moonshot [ADDIN EN.CITE <EndNote><Cite><Author>Mitchell</Author><Year>2016</Year><RecNum>40</RecNum><DisplayText>(Mitchell, 2016)</DisplayText><record><rec-number>40</rec-number><foreign-keys><key app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs" timestamp="1470324343">40</key></foreign-keys><ref-type name="Journal Article">17</ref-type><contributors><authors><author>Edith Mitchell</author></authors></contributors><titles><title>Moonshot Toward a Cure for Cancer</title><secondary-title>Journal of the National Medical Association</secondary-title></titles><periodical><full-title>Journal of the National Medical Association</full-title></periodical><pages>104–105</pages><volume>108</volume><number>2</number><dates><year>2016</year></dates

567 ><urls></urls></record></Cite></EndNote>], high-throughput approaches could screen a large
568 set of chemicals for potential carcinogenicity and identify a suite of chemicals for additional
569 animal toxicity testing. Examining noncancer endpoints may also be challenging, which is why
570 developing AOPs and networks to contextualize and interpret non-apical hazard data in relation
571 to population health is of increasing value. Epidemiology studies can be designed to inform and
572 validate high-throughput testing approaches by identifying both chemical stressors and
573 nonchemical stressors that modify responses to chemical exposures and also to test relationships
574 between disease and early markers of exposure and biological response (e.g., epigenetic
575 changes).

576 ***Better understanding the impact of cumulative exposures:*** While cumulative risk assessment
577 has been of high interest for the past few decades, putting cumulative assessment approaches
578 into practice has been challenging. This framework provides a new construct for considering
579 cumulative risk. By focusing on a health endpoint of concern, one could consider the multiple
580 exposures that may contribute to a health outcome. Past NRC recommendations have
581 encouraged assessors to evaluate the combined effects of exposures to all chemicals that affect
582 a common adverse outcome, for example, male reproductive development [ADDIN EN.CITE
583 <EndNote><Cite><Author>National Research
584 Council</Author><Year>2008</Year><RecNum>9</RecNum><DisplayText>(National Research
585 Council, 2008)</DisplayText><record><rec-number>9</rec-number><foreign-keys><key
586 app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs"
587 timestamp="1468525915">9</key></foreign-keys><ref-type name="Report">27</ref-
588 type><contributors><authors><author>National Research
589 Council,</author></authors><tertiary-authors><author>The National Academies
590 Press,</author></tertiary-authors></contributors><titles><title>Phthalates and Cumulative Risk
591 Assessment: The Tasks Ahead</title></titles><dates><year>2008</year></dates><pub-
592 location>Washington, D.C.</pub-location><urls></urls></record></Cite></EndNote>].
593 Challenges include gaining adequate understanding of individual chemical impacts in order to
594 group chemicals by health outcome. Increased research into the biological pathways by which

595 chemicals affect health status can help inform approaches for estimating the joint effect of
596 chemicals without testing all permutations or combinations.
597
598 One possible example of an alternative approach is Health Impact Assessment (HIA), which uses
599 a systems approach to array data sources and analytic methods and considers input from
600 stakeholders to determine potential effects of a proposed action or decision on the health of a
601 population and the distribution of those effects within the population [ADDIN EN.CITE
602 <EndNote><Cite><Author>National Research
603 Council</Author><Year>2011</Year><RecNum>41</RecNum><DisplayText>(National Research
604 Council, 2011)</DisplayText><record><rec-number>41</rec-number><foreign-keys><key
605 app="EN" db-id="xdrxape2fvv5fkefa9avdd58pttw9a9se9zs"
606 timestamp="1470324571">41</key></foreign-keys><ref-type name="Report">27</ref-
607 type><contributors><authors><author>National Research
608 Council,</author></authors><tertiary-authors><author>The National Academic
609 Press,</author></tertiary-authors></contributors><titles><title>Improving Health in the United
610 States: The Role of Health Impact
611 Assessment</title></titles><dates><year>2011</year></dates><pub-location>Washington,
612 D.C.</pub-location><urls></urls></record></Cite></EndNote>]. Using HIA approaches for
613 chemical risk assessments done through this framework can offer a method to organize various
614 data streams that can influence our understanding of a health impact, inform potential multiple
615 contributors to adverse health outcomes, and provide recommendations to decision makers on
616 monitoring and managing these outcomes.
617
618 ***Consider public health concepts such as attributable or relative risk***: This new approach takes a
619 systematic view of collective factors that contribute to a health outcome or disease state,
620 including those that are not regulated by one single federal entity. Any single health outcome
621 may be influenced by multiple factors beyond chemical exposures, such as nutrition, genetics, or
622 social stressors. Because those factors are not regulated, it is important for environmental
623 regulatory agencies to understand what fraction of the disease burden is influenced by the

624 regulated environmental exposure. Public health approaches, such as attributable risk, can help
625 inform this understanding. Challenges may include incorporating these approaches, which are
626 typically used in epidemiology, to animal and advanced toxicity testing data, ensuring adequate
627 training with the approaches, and communicating risk in a way that acknowledges the influence
628 of non-regulated factors.

629 **Conclusions**

630 Understanding the health effects of chemicals has real implications for public health. This
631 proposed approach for chemical risk assessment starts at the health endpoint and incorporates
632 multiple data streams, including data developed using newer technologies such as high-
633 throughput screening. In parallel with more traditional risk assessment approaches, this will lead
634 to a better understanding of mechanisms of single chemicals as well as cumulative exposures
635 that lead to specific disease endpoints. This new lens will need to be applied to the complete risk
636 assessment process, including problem formulation, data considerations, and data synthesis
637 through multi-pathway methods, including cumulative assessment and health impact
638 assessment, with an eye to prevention of adverse effects. This approach draws upon the best
639 available science to improve our understanding of the health impacts of environmental chemicals
640 and informs decision making to prevent, reduce, or mitigate exposure and ultimately improve
641 public health.

642

643 **References**

644 NRC 2016; placeholder for report from: http://dels.nas.edu/Study-In-Progress/Incorporating-
645 21st-Century-Science-into-Risk/DELS-BEST-14-04?bname=best

646 Add references to ENDNOTE

647 Lowy and Collins 2016: DOI: 10.1056/NEJMp1600894

648 Replace Weinhold with

649 Institute of Medicine. [HYPERLINK "http://www.nap.edu/catalog/10839/reducing-birth-defects-
650 meeting-the-challenge-in-the-developing-world"] **(2003)**

651 U.S. EPA 2010. Guidelines for Preparing Economic Analyses. EPA 240-R-10-001. [HYPERLINK
652 "https://www.epa.gov/environmental-economics/guidelines-preparing-economic-analyses"]

653

654 [ADDIN EN.REFLIST]

655

Figure Legends

Figure 1. Conceptual Model for a Public Health Perspective for Chemical Risk Assessment

This conceptual model illustrates how the starting point in a public-health focused risk assessment would differ from that of traditional risk assessment. In traditional risk assessment, the starting point is focused on specific chemicals or classes of chemicals of concern, with multiple data streams informing what are the critical effects from that chemical. A public health perspective would focus on the adverse health outcome of concern with multiple data streams informing our understanding of hazard and exposure in the context of public health decisions related to that outcome, and not necessarily focused on just one chemical or class of chemicals.

Figure 2. Adverse Outcome Pathway for Cardiovascular Outcomes. This figure illustrates the biological pathway leading from exposure to adverse cardiovascular outcomes for a variety of chemicals. On the left hand side of the figure these pathways are linked to the AOP whereas on the right hand side of the figure we see the traditional risk factors for adverse cardiovascular outcomes.